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Phase I Cancer Trials and Palliative Care: Antagonism, Irrelevance, or Synergy?

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Special Article**15-00445R1****Phase I Cancer Trials and Palliative Care: Antagonism, Irrelevance, or Synergy?**

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Abstract

This paper synthesizes the presentations and conclusions of an international symposium on phase 1 oncology trials, palliative care, and ethics held in 2014. The purpose of the symposium was to discuss the intersection of three independent trends which unfolded in the past decade. First, large-scale reviews of hundreds of phase I trials have indicated there is a relatively low risk of serious harm, and some prospect of clinical benefit that can be meaningful to patients. Second, changes in the design and analysis of phase I trials, the introduction of “targeted” investigational agents that are generally less toxic, and an increase in phase I trials that combine two or more agents in a novel way, have changed the conduct of these trials and decreased fears and apprehensions about participation. Third, the field of palliative care in cancer has expanded greatly, offering symptom management to late-stage cancer patients, and demonstrated that it is not mutually exclusive with disease-targeted therapies or clinical research. Opportunities for collaboration and further research at the intersection of phase 1 oncology trials and palliative care are highlighted.

Key Words: Palliative care, phase I clinical trials, cancer, ethics, informed consent, end-of-life care

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Introduction

The ethical and clinical issues regarding early phase cancer trials have been debated for more than two decades.¹⁻¹⁰ They include concerns that desperate patients may regard phase I trials as therapeutic and that researchers could reinforce this misconception by de-emphasizing the trials' true intent to study the safety of investigational agents. Recent early phase trials demonstrating remarkable therapeutic response¹¹ may have increased patient perception that phase I clinical research is an extension of clinical care.¹²⁻¹³ At the same time, the field of palliative care (PC) has grown rapidly, is now recognized as a specialty, and randomized trials have documented several improved clinical outcomes with palliative care.¹⁴⁻¹⁹ Consequently, experts and professional organizations have recommended increased integration of oncology care and palliative care early in the illness of patients with metastatic cancer.²⁰⁻²¹ Extension of this simultaneous, integrated care model to patients in early phase trials may address some of the central clinical and ethical challenges surrounding phase I trials. Although palliative care and phase I trials were considered to have a dichotomous relationship in the past, the changing nature and expansion of both fields has started to transform this relationship.²² We recently convened an international panel of experts to discuss this shift in phase I oncology and palliative care science and the implications for clinical care and ethics.

Ethical Challenges

Informed Consent

Key aspects of informed consent for patients enrolling in clinical trials are the assessment of potential harms and their probability of occurring, set against the potential benefits and their probability. Early-phase oncology trials are an important step in developing more effective therapies for treating individual cancers. Yet these trials promise little or no direct clinical

benefit to those who participate in them. Since these trials are designed to test toxicity rather than the efficacy of investigational agents, patients should expect to incur some risks and no or little clinical benefit from participating. However, a significant body of research indicates that many participants believe that they will experience a substantial personal health benefit by enrolling.²³⁻

²⁶ This fact has been a source of concern for ethicists and researchers.

Of particular concern is the impact high patient expectations have on informed consent to participate in this form of research. Early studies²⁷ focused on the possibility that patients have an inadequate understanding of the nature of the trials in which they participate. Many participants seem to be under the so-called “therapeutic misconception.” They believe incorrectly that the primary purpose of phase I trials is to provide them with direct clinical benefit rather than advancing generalizable scientific knowledge.²⁸ Later research suggests that patients in phase I oncology trials simply miscalculate their own prospects for benefit, even though they fully understand the nature and purpose of research. This misunderstanding is referred to as the “therapeutic misestimation.”²⁹ However, in recent years, researchers have begun to investigate the possibility that high expectation for personal benefit in these trials does not reflect any deficit in understanding at all. Rather, in reporting high expectations for benefit, patients may be expressing optimism about their participation in the trial. This phenomenon has been termed “therapeutic optimism.”³⁰⁻³¹ Some writers have suggested that therapeutic optimism is mere hopefulness. On this view, patients are not reporting expectations for benefit at all, but rather are making statements about what they hope will happen.³²⁻³⁴ This explanation overlooks evidence that indicates that therapeutic optimism reflects a bias that distorts the processing and appreciation of risk/benefit information. This bias is referred to as “the optimistic bias” or “unrealistic optimism.”³⁵ This bias has not generally been correlated with a hopeful outlook on

life and has been found to be consequential for behavior.³⁶ [All these explanations for why patients might report high expectations for personal clinical benefit from participating in phase I cancer trials raise concerns about the quality of their consent to participate in research.

Vulnerability, Autonomy, Non-Maleficence

Other important ethical issues regarding Phase I trials include the perceived vulnerability of patients and the need to promote their well-being while respecting their autonomy. Patients who are referred to participate in a phase I study face challenging decisions, having to weigh potential benefits of a new investigational intervention and unknown side effects including potential harm. Patients considered for enrollment into these studies have commonly undergone exhaustive anti-cancer therapies, and in most cases standard treatments have failed to work. In addition, a considerable amount of patients are suffering from long term adverse events related to prior therapies, including neuropathy, alopecia, and bone marrow toxicity, or they have symptoms related to their underlying disease. Interestingly, despite these side effects, patients with a prior history of systemic therapy may be more likely to enroll in phase I trials than those who have not received systemic therapy.³⁷

Since impaired physical, emotional and social functioning have all been associated with therapeutic misconception, phase I trial candidates may need additional care to avoid this form of misunderstanding.³⁸ Expressions of therapeutic optimism by these candidates, when it reflects optimistic bias and not mere hopefulness, should also be of concern. Although the risks to these patients should not be discounted, neither should they be overprotected. Patients may want to participate in research for personal and altruistic reasons.³⁹ Participants in later stage trials commonly report that altruism contributed to their decision to enroll, but participants in phase 1 trials rarely report altruism as their *primary* motivation for study participation.⁴⁰

Palliative Care and Phase I: Antagonism, Irrelevance, or Synergy?

The potential *relevance* of palliative care for phase I participants is based on their prognosis and symptom burden. Patients enrolled in phase I trials have a median survival of about nine months⁴¹⁻⁴² and are likely to be symptomatic from their disease or prior treatments. Patients have traditionally exhausted conventional therapy and later-phase clinical trial options. These are precisely the same characteristics of many patients referred to specialist palliative care. Of those patients referred for phase I trial consideration, a significant proportion are too sick and frail for enrollment; these patients have a demonstrable need for optimal symptom management and end of life care. Poor or deteriorating performance status is responsible for recruitment failure in 25-35% of patients referred to early phase trial programs.⁴³⁻⁴⁴

Even with targeted investigational agents, many phase I participants will experience a broad range of symptoms and side effects. These side effects may range from standard side effects (e.g., pain and mucositis as a result of cytotoxic therapy), to new and emerging adverse events as a result of targeted therapies. Although phase I programs have made progress with new targeted drugs that match tumor biology and spare patients exposure to potentially inactive drugs, targeted investigational agents have been reported to cause side effects such as fatigue,⁴⁵ cachexia,⁴⁶ hypothyroidism,⁴⁷ and hypogonadism.⁴⁸ These symptoms should be addressed, possibly with the aid of specialist palliative care, in order to improve quality of life, decrease symptom burden, and enable patients to complete their investigational treatment.

Two retrospective studies from palliative care clinics at U.S. comprehensive cancer centers found high symptom expression in phase I patients, similar to other ambulatory patients referred by non-phase I oncologists.⁽⁴⁹⁻⁵⁰⁾ Compared with other patients who had cancer, those

participating in phase I trials were less likely to require home care services, despite experiencing a great symptom burden. The cohort study from M. D. Anderson's supportive care clinic found no difference between these groups for the interval between registration at the cancer center and palliative care consultation. Survival was similar between the two groups, however, performance status was better in phase I patients ($P=.003$).

This simultaneous, concurrent approach to palliative care and phase I also may stimulate goals of care discussions with patients,⁵¹ which ideally should occur before deciding to pursue phase I treatment. The palliative care consultation should not itself be part of the informed consent process for research but rather a precursor, aimed at clarifying goals of care and addressing symptom management needs. To be sure, this requires patients to be aware of the differences between a palliative care-only strategy and an anti-cancer strategy. The point of the consultation is not, however, to advocate for one or the other strategy but to clearly discuss the options so that the patient can make an informed choice.

Despite this common ground, the relationship between phase I oncology trials and palliative care to date has often been viewed by stakeholders in both fields as mutually exclusive or even *antagonistic*.⁵²⁻⁵³ Trialists may also choose to refer to internists and specialists such as psychiatry rather than palliative care in order to address patient needs. However, this “congress” model⁵⁴ of care involving multiple sub-specialists is likely to increase the fractured nature of care already experienced by many cancer patients. Confusion about coverage requirements might also encourage the belief that phase I trials and palliative care are mutually exclusive. In the U.S., the Medicare “hospice benefit” mandates patients seeking comfort care forgo clinical research as well as disease-focused conventional therapies, so that palliative care and phase I could only be sequential but not concurrent, reifying antagonism and zero-sum thinking. There is a need to

transform the model of treatment of advanced cancer so that oncologic and palliative care are delivered simultaneously and collaboratively by specialist palliative care teams and oncologists. While the mutual exclusivity of the Medicare hospice benefit may be unique to the U.S., the more general issue of the ways in which antagonism has been encouraged by regulatory bodies, traditional practice models, and relationships between the specialties needs to be explored and perhaps changed in many countries. Outside of hospice in the U.S., innovative models of care such as home palliative care⁵⁵ and palliative care ambulatory clinics may be templates for providing early palliative care concurrently with oncologic treatments.⁵⁶ The financial sustainability of such models is also an issue, at least in the revenue-centric model of healthcare in most settings in the U.S.⁵⁷

Opportunities for Collaboration

Based on discussion between phase I trialists, ethicists and palliativists at the Brocher Symposium, we identified six areas for collaboration and potential synergy between phase I oncology trials and palliative care.

Target Areas

Earlier Identification & Referral. Early referral to palliative care for simultaneous management has been shown to improve clinical outcomes and survival.⁵⁸ It may be useful for phase I oncology trialists and specialist palliative care teams to develop criteria and methods for identifying patients in order to trigger prompt earlier referral by oncologists. Ideally, all phase I-eligible patients should be referred for palliative care, and this should not be seen as a barrier to phase I participation. Those patients not eligible for phase I trials because of poor performance status are also likely to benefit from specialist palliative care. Objective (e.g., albumin, metastatic

sites, CRP, LDH⁵⁹⁻⁶⁰) and subjective (e.g., performance status, patient reported outcomes such as symptoms⁶¹ and quality of life⁶²) prognostic factors have been used to identify patients who are suitable for enrollment in phase I programs.

Patient Assessment. There is value in phase I programs incorporating palliative care team members in the informed consent process to help ensure participation is in concordance with patients' preferences and values. This can also set the stage for more intensive palliative care involvement as patients become more symptomatic. They will have become familiar with palliative care and develop an understanding that undergoing palliative care does not amount to forgoing anti-cancer treatment. This would contribute to the validity of consent, especially for cases where the comprehension of the information about the phase I trial is less than ideal.

Maintaining Function. Contemporary palliative care clinicians are focused on maintaining or restoring function (performance status). This is of great interest not only to patients, but also to phase I researchers both in terms of helping with eligibility and enabling participants to complete trials¹. However, contemporary palliative care requires substantial resources in nutrition, exercise, and other rehabilitative domains. Interdisciplinary outpatient clinics with counselors, psychologists, and dietitians have been established with success at selected cancer centers in the U.S.⁶³

Symptom Management. Phase I oncology trials often produce symptoms and side effects, and palliative care clinicians may bring much-needed expertise in symptom management that might not be in the repertoire of phase I trialists. Also, the newer investigational agents explored in phase I trials, including immunotherapy, may be less cytotoxic but still produce side effects such as skin rashes, severe diarrhea, endocrine dysfunction, and sometimes lead to novel adverse

events, such as auto-immune disorders. Adequately describing these events and developing strategies for their management could be an interesting joint research effort for trialists and palliative care clinicians.

Measurement of Patient-Reported Outcomes (PROs). Palliative care researchers have created several low-burden scales for assessing symptoms and other outcomes that are well validated.^{64,65,66} Phase I trialists agreed at the symposium that the primary endpoints for phase I trials are too narrowly defined in terms of safety and dosing, with secondary outcomes of tumor response that are even narrower (e.g., RECIST criteria for most solid tumors). Palliative clinician-researchers could provide guidance in selecting and measuring patient-reported outcomes that would make assessment of harms and benefits of investigational agents more complete. This may be especially helpful with new treatment modalities that have more chronic, low-intensity symptoms and side effects.

Seamless Transitions. Even with the changing treatment paradigms in oncology, many if not most phase I trial patients will continue to be patients with advanced disease and limited prognosis. Phase I trialists can work with the clinical oncologists to introduce palliative care concepts and team members before, during, and after trial participation. This could ensure a more seamless transition to hospice or predominant palliation as needed.

A number of these six target areas would not only potentially improve patient care and early phase research, but also help to find common ground for further research collaboration among oncologists, clinical investigators, palliative care specialists, and ethicists. For example, collaborative research could test different ways of integrating palliative care in the assessment and consent processes, or explore the value of measuring PROs more systematically.

Characteristics of Good Collaborators

There are several characteristics phase I trialists and palliativists may consider ideal for a successful collaborative relationship (Table 1). The characteristics shown in Table 1 are a mixture of technical expertise as well as values and orientation. It may be easier to change technical skills and clinical knowledge than to alter values or philosophy. Perhaps the issue of greatest concern between the two groups (trialists and palliativists) is regarding their perceptions of what they are trying to talk patients into, or out of. It is certainly within the legitimate role of trialists to be recruiting patients for their studies; in that sense, they are advocates for continued treatment in the research setting. Phase I trialists would expect palliativists to refrain from ‘talking’ patients out of trials. From the other perspective, palliativists should expect phase I trialists not to ‘talk’ patients *into* pursuing the trial to the detriment of good clinical care. Palliativists will advocate for good symptom management regardless of which strategy the patient opts to pursue.

Evolution of Phase I Trials and Palliative Care

Phase I oncology trials and palliative care are both dynamic, rapidly changing fields and there is a risk when describing the relationship between and two entities of assuming that those entities are unchanging. In Table 2, these two fields are characterized in terms of their traditional and contemporary models, contrasting traditional aspects in the upper half of the table with contemporary aspects in the lower half. The contemporary model adds to the traditional model and is often a hybrid rather than a complete replacement.

Changes in Phase I oncology studies have been extensive over the past decade and include better understanding of tumor biology and development of targeted interventions.⁶⁷⁻⁷³

Sparing participants from exposure to investigational agents and potential harm when they do not have the specific underlying tumor biology has been a major advance. While the selection of patients for trials based on molecular markers has obvious benefits, there are also potential pitfalls.⁷⁴ For example, patients that do not express the biomarker may still have benefited from a particular therapy. The implicit search for clinical benefit may also be more pronounced among patients who know their tumors have particular molecular characteristics that may make them targets for particular kinds of agents.⁷⁵

Another recent development is in the use of preclinical predictive pharmacokinetic models that are more sophisticated, providing the ability to predict an active drug level prior to phase-I start. Also, new clinical trial designs, such as “accelerated dose escalation” to spare patients from potential “under dosing.” Lastly, there have been significant increases in accrual sizes of some phase I studies, generally under the criterion as a “phase Ib” or “expansion phase” component of a traditional phase I study. In these scenarios, there may be hundreds of patients treated at the same or limited range of doses,⁷⁶ and have even led to FDA approval of an agent following a successful phase 1 study expansion outcome.⁷⁷ In the expansion phase of the phase I study of ceritinib in ALK mutated non-small cell lung cancer, the response rate was 58%, superior to most therapies in lung cancer, and far surpassing typical expectations from a traditional phase I study.⁷⁷ These types of studies have many similarities to conventional single arm phase II studies, and begin to blur the lines between traditional phase I dose escalation studies and the much larger safety & efficacy phase I expansion studies. Attention to the type of phase I study being employed, and the quality of the drug target/agent used may have implications on a patient’s expectation of personal benefit, and should be taken into consideration.

For the palliative care field, there are several implications of these unfolding changes in phase I trials. Palliative care specialists should not assume that all phase I participants have exhausted conventional therapies and are in the final stages of their disease. They should be prepared for a wide variety of side effects and symptoms that include and go beyond those traditionally seen in cytotoxic therapies. They should understand the nuances of patients' expectations and hopes about early phase trials, and how those may have been shaped by accounts of astounding responses to early phase agents as presented in popular media.

The palliative care field, too, is dynamic and evolving. There is a greater emphasis on palliative care supporting patients' survival and life, and not just a focus on a good, comfortable death. Palliative care is increasingly seen in ambulatory clinics and in home visit programs, for patients who may be months or even years away from demise. Payors and providers are experimenting with ways to encourage this earlier, concurrent model of palliative care. The most important implication of this for phase I trialists is that contemporary palliative care specialists may be even more likely to be good partners, less antagonistic toward treatment and trials for patients with advanced disease. Another implication is that palliative care specialists are becoming more commonly seen in the same ambulatory clinics where oncologists and phase I trialists are working with patients, and this greater access can be used for more timely and concurrent care.

Moving Forward

In the future, several issues concerning the relationship between Palliative Care and Phase I oncology trials will need to be explored if we are to achieve an integrated care model for patients entering early phase studies. Phase I trialists may need to develop skills as primary

palliativists since there are insufficient numbers of palliative care physicians being trained to cope with current needs.⁷⁸ Perhaps brief pragmatic symptom assessments used in palliative care, such as the ESAS may prove to be useful within phase I oncology clinics. Since patients too infrequently alert their care teams about all of their symptoms, systematic inquiry is necessary to identify symptom burden as it develops.⁷⁹ In a standardized population-wide study, the Edmonton Symptom Assessment System (ESAS) detected a high prevalence of multiple symptoms in ambulatory cancer patients similar to those reported in palliative care populations.⁸⁰

Palliative care teams also may need training specific to oncology and phase I trial demands. They should be educated, as needed, about the evidence indicating that participants are not necessarily making ill-informed decisions. If they are staunchly antagonistic to early phase cancer trials, then perhaps an academic cancer center is not the right setting for them. Palliative care specialists in academic cancer centers should familiarize themselves with the early phase trial protocols with attention to the potential symptoms and side effects of the agents being tested, and the extent to which any palliative treatments would be contra-indicated, if any.

Both groups are advocates for earlier referral, and mandatory co-management with palliative care should be considered once a patient with advanced disease is referred to phase I trials. Using predictive analytics of existing clinical and utilization data on patients to prompt oncologists that a patient might be an appropriate candidate for palliative care and phase I trials may be a useful strategy. There is also a potential for empowering patients to better assess and interpret the likelihood of benefit or harm by developing decision aid tools in the informed consent process. As phase I trials shift from a traditional model, and palliative care consultations are initiated before phase 1 trial enrollment, research is needed to determine whether patients experience more or less misestimation or misconception of therapy, unrealistic optimism, or

other biases and errors of comprehension. The impact of palliative care in clinical and ethical outcomes will need to be evaluated as well, including recruitment into trials, completion of the investigational regimes, maintenance of performance status, improved comprehension of the consent process, and the documentation of values and preference. Finally, there is potential for closer cooperation between palliative care and phase I oncology researchers regarding expansion of secondary endpoints in phase I trials to include patient reported outcomes or other outcomes relevant to palliative care (e.g., phase I agent found to have an anti-cachectic effect⁸¹).

Conclusion

Both phase I and palliative care are rapidly changing in response to patient demographics, societal expectations, and cancer science and trials. The changes in phase I oncology trials have important implications for timing of referral, patients' perceptions of the intent and potential outcome of participating, ethics, and palliative care. Similarly, the changes in models of palliative care will have an impact on engagement and integration with phase I oncology programs.

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Table 1. Characteristics of Successful Collaborative Relationships

What phase I trialists seek in a palliative care partner	What palliativists seek in a phase I partner
Expertise in maintaining/restoring PS	Awareness of value and role of specialist PC
Expertise in symptom management	Elicit and respect patient preferences
Providing a safety-net for patients with progression	Early, simultaneous referral of patients
Expertise in measuring PROs	Consideration of PROs as secondary outcomes
Available and responsive in the outpatient setting	Value evidence-based symptom management
Familiarity with and support of phase I trials and clinical research	Patient engagement and non-abandonment
Interest in possible research collaboration	Interest in possible research collaboration

PRO = patient-reported outcome; PS=performance status; PC=palliative care

Table 2. Characterization of Phase I Science and Palliative Care Evolution ^a

Evolution of Palliative Care and Early Phase Oncology Trials in the Changing Environment of Cancer Care and Drug Development		
	Early Phase Trials	Palliative Care
Traditional	<ul style="list-style-type: none"> • “Phase I” • Collect data on safety and dosing • After conventional treatment, typically towards the end of life • Single cytotoxic investigational agent • No therapeutic intent or expectation <p><i>Ethical issues: consent, vulnerability, harms & benefits, misperception of intent and clinical benefit</i></p>	<ul style="list-style-type: none"> • “Hospice” • Comes after cancer-fighting treatment • Quality of dying and death • Opposition to over-treatment of cancer • Response to medicalization and reductionism • Separate places, teams • Assume further decline is irreversible <p><i>Ethical issues: futility, moral distress, avoiding harm</i></p>

Contemporary

- “Early phase”
- Collect data on safety, dosing and therapeutic effect
- Earlier, possibly first line of “treatment”
- Combined investigational agents and new classes of agents (e.g. targeted)
- Some therapeutic intent or expectation and more “miracle hype”

Ethical issues: Same as above, but more complex, especially regarding the intent of trials

- “Palliative / supportive care”
- Earlier and simultaneous with cancer-fighting treatment
- Greater focus on living with advanced cancer (continued support of the dying)
- Open to oncological treatment for palliative purposes
- Variety of models, settings
- Efforts to maintain & restore function, strength

Ethical issues: Beneficence and justice (ensuring more widespread access)

^a Based on Brocher Symposium presentations and discussion.

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